REMARKS

The Examiner stated that claims 1-12 are pending in the instant application. Claims 7-12 have been withdrawn, and claims 1-6 are currently under examination.

Priority

Applicants amendment to the specification to update the priority claim is acknowledged.

Objection to the Specification

The previous objection to the specification is withdrawn in view of Applicants' amendment.

Withdrawn Rejections

The rejection of claims under 35 U.S.C. § 112, second paragraph is withdrawn in view of Applicants' amendment.

35 U.S.C. § 101, Rejection of Claims 1-6

The Examiner has maintained the rejection of claims 1-6 under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons of record in the previous Office Action, Paper No. 9, pages 3-6 and below.

The Examiner stated that Applicants' arguments in response to the previous Office Action have been considered but are not considered persuasive. Although the protein of the instant invention may be a G-protein coupled receptor, the Examiner stated, it is not predictable what the function of any GPCR is from this information. The GPCRs do not have a common practical utility which is based upon a property common to all members of that class. Though the protein of the instant invention may be classified as a member of the GPCR superfamily, this does not automatically confer a specific and substantial utility to the protein, since there is extreme diversity in the activities and biological functions of these proteins.

The Examiner also stated that Applicants arguments relative to an asserted utility for the claimed polynucleotide of SEQ ID NO:7 as a diagnostic for cancer, in particular, follicular carcinoma of the thyroid, have been considered but are not persuasive. The Examiner stated that use of the claimed polynucleotide as a cancer diagnostic would be a specific and substantial use if a correlation were found between the molecules of the invention and follicular carcinomas.

However, the Examiner stated, the only correlation supporting the asserted utility is based on expression of the gene in one single library. The Examiner then cited the National Cancer Institute (NCI) Guidelines for Marker Development as evidence of the requirements for preliminary identification of a potentially useful marker.

Applicants Response

Applicants reiterate arguments presented in the previous response filed 1/14/2003 that the instant specification, as well as the priority application, USSN 09/156,513 (filed 9/17/1998) adequately characterizes SEQ ID NO:1 not only as a G-protein coupled receptor (GPCR), but a likely member of the subfamily of metabotropic GPCRs. Applicants further dispute the Examiners' contention that membership in a family of notably useful proteins, such as GPCRs, does not impute a specific and substantial utility to the new member, merely because all family members do not possess a common utility.

Membership in a Class of Useful Products Can Be Proof of Utility

Despite the uncontradicted evidence that the claimed polynucleotide encodes a polypeptide in the GPCR family, in particular, the metabotropic GPCR subfamily, the Examiner refused to impute the utility of the members of the GPCR family to SEQ ID NO:1. In the Office Action, the Patent Examiner takes the position that, unless Appellants can identify which particular biological function within the class of GPCRs is possessed by SEQ ID NO:1, utility cannot be imputed. To demonstrate utility by membership in the class of GPCRs, the Examiner would require that all GPCRs possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial

likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Examiner addresses SEQ ID NO:1 as if the general class in which it is included is not the GPCRs family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the GPCR family does not. The GPCR family, and in particular, the metabotropic subfamily of GRCRs. is sufficiently specific to rule out any reasonable possibility that SEQ ID NO:1 would not also be useful like the other members of the family.

Because the Examiner has not presented any evidence that the metabotropic class of GPCRs has any, let alone a substantial number, of useless members, the Examiner must conclude that there is a "substantial likelihood" that the SEQ ID NO:1 encoded by the claimed polynucleotide is useful. It follows that the claimed polynucleotide, SEQ ID NO:7, also is useful.

Applicants also reiterate that the asserted utility for the polynucleotide encoding SEQ ID NO:1 in the detection and diagnosis of follicular carcinoma of the thyroid, based on a significant (4-fold) differential expression in that disease condition, is both specific, substantial, and credible. The Examiners' continued allegation that the asserted utility is not credible because it is based on expression of the transcript in only one library ignores the fact that, as previously pointed out, a number of thyroid libraries were examined representing both normal and diseased thyroid, and that only libraries associated with thyroid cancer were found to express the gene. In particular, the gene was most highly expressed in a thyroid follicular carcinoma tumor library (THYRTUP02), but was also expressed in a library associated with follicular adenoma (THYRNOT03), a precancerous condition to follicular carcinoma. Such evidence provides more than a "substantial likelihood" that the polynucleotide may be used in the detection and diagnosis of the disease. The Examiners' reliance on references such as the NCI Guidelines for Marker Development to support her position is merely an attempt to raise the standard for utility to one of near certainty. However, the standard applicable in this case is not proof to certainty, but

rather proof to reasonable probability. *Brenner*, 383 U.S. at 532.

In addition, the Examiner has ignored a well-established utility for the claimed invention in gene expression profiling studies in toxicology that would be readily apparent to the skilled artisan at the time the instant application was filed. In support of this well-established utility, applicants have attached a declaration under 37 CFR 1.132 of Dr. John C. Rockett. The Rockett declaration describes, in particular, how the claimed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing toxicological profiles for potential toxicants. Dr. Rockett states, for example, in ¶ 15, bottom of page 8 of the declaration that, with reference to well-characterized toxicants:

> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by such toxicants, this would appear a longer term goal, as the majority of human genes have not been sequenced, far less their functionality determined. However, the current use of gene profiling yields a *pattern* of gene changes for a xenobiotic of unknown toxicity which may be alerting the toxicologist to possible *in vivo* similarities between the unknown and the standard ... (original emphasis).

Thus, the use of the claimed polynucleotides in gene expression profiling for potential toxicants represents a well established use independent of any functionality for the encoded polypeptide or known mechanism of toxicity for the encoded polypeptide.

For all of the above reasons, applicants submit that both specific and substantial, well-established and asserted utilities for the claimed invention are readily apparent from, and specifically disclosed in the specification and therefore request withdrawal of the rejection of claims 1 and 3-12 under 35 U.S.C. § 101.

35 U.S.C. § 112, First Paragraph, Rejection of Claims 1-6

The Examiner has maintained the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility fr the reasons set forth above, one skilled in the art would clearly not know how to use the claimed invention.

The Examiner has also rejected claims 1-6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which is not described in the specification in such a was as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention.

The Examiner stated that while the specification describes a polypeptide sequence consisting of SEQ ID NO:1, the claims encompass polypeptides comprising fragments and homologues that vary substantially in length and also in amino acid composition. The instant disclosure of a single polypeptide, that of SEQ ID NO:1, does not support the scope of the claimed genus, which encompasses a substantial variety of subgenera. The Examiner cited *Reagents of the University of California v Eli Lilly* with respect to the premise that "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or a recitation of structural features common to the genus, which features constitute a substantial portion of the genus". The Examiner then cited various references alleging to support the unpredictability of protein function based on sequence homology. See, in particular, Vukicevic et al.; Tischer et al.; and Kopchick et al. The Examiner concluded by saying that given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus, it cannot be established that a representative number of species have been disclosed by the claims. Further, the Examiner stated, no activity is set forth for the additional sequences.

Applicants Response

With respect to fragments of SEQ ID NO:1, as recited in claim 1, applicants submit that the recited fragments are specifically disclosed in the claims and do not therefore "vary substantially in length and also in amino acid composition" beyond what is specifically disclosed.

The claimed "homologues" of SEQ ID NO:1 referred to by the Examiner presumably relate to variants of SEQ ID NO:1 and SEQ ID NO:7, as recited in claims 1 and 2, respectively. Applicants submit that the polypeptides and polynucleotides of the invention, including the recited variants, are adequately described in accordance with 35 U.S.C. § 112, first paragraph, and supported by relevant case law, some of which is referred to by the Examiner.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that :

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

SEQ ID NO:1 and SEQ ID NO:7 are specifically disclosed in the priority application Serial No. 09/156,513 (see, for example, page 2, lines 34-37 and page 3, lines 13-14). Variants of SEQ ID NO:1 and SEQ ID NO:7 are described, for example, at page 2, line 38 through page 3, line 2. In particular, the preferred, more preferred, and most preferred variants (80%, 90%, and 95% amino acid sequence similarity to SEQ ID NO:1) are described, for example, at page 12, lines 13-16 of priority application Serial No. 09/156,513. Incyte clones in which the nucleic acids encoding the human HGPRP-1 (SEQ ID NO:1) were first identified and libraries from which those clones were isolated are described, for example, at page 11, lines 24-30 and Table 1 of the priority application. Chemical and structural features of SEQ ID NO:1 are described, for example, on page 11, lines 31-35 and Table 2 of the priority application. Given SEQ ID NO:1, one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:1 having at least 90% sequence identity to SEQ ID NO:1. Accordingly, the Specification provides an adequate written description of the recited polypeptide sequences.

A. The Specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1.

The Office Action has further asserted that the claims are not supported by an adequate written description because:

> Claims 1-6 contain "subject matter which is not described in the specification in such a was as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention".
>
> (page 8 of the Office Action of present Office Action)

Such a position is believed to present a misapplication of the law.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind to the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics. For example, the "variant language" of independent claim 1 recites chemical structure to define the claimed genus:

> 1. An isolated cDNA comprising a nucleic acid encoding an amino acid sequence selected from:...c) a variant of SEQ ID NO:1 having at least 90% amino acid sequence identity to SEQ ID NO:1...

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides or polypeptides recited by the claims. In fact, there is no recitation of functional characteristics. Moreover, if such functional recitations were included, it would add to the structural characterization of the recited polynucleotides or polypeptides or. The polynucleotides or polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis

of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as highly variant, i.e., "encompassing a substantial variety of subgenera" (Office Action, page 8). Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078), also cited at page 29 of the instatn application. Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to GPCR proteins, in particular, metabotropic glutamate GPCR proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al, naturally occurring molecules may exist which could be characterized as metabotropic glutamate GPCR proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, polynucleotides encoding "an amino acid sequence having at least 90% amino acid sequence identity SEQ ID NO:1" (note that SEQ ID NO:1 has 441 amino acid residues). This variation is far less than that of all potential metabotropic glutamate GPCR proteins related to SEQ ID NO:1, i.e., those metabotropic glutamate GPCR proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the

benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of September 17, 1998. Much has happened in the development of recombinant DNA technology in the 20 or more years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:7, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

4. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 or SEQ ID NO:7. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides or polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

35 U.S.C. § 102(b), Rejection of Claims 1 and 3-6

The Examiner has maintained the rejection of claims 1 and 3-6 under 35 U.S.C. § 102(b), as anticipated by Valenzuela et al., WO 99/55721, November 4, 1999, for the reasons of record in the previous Office Action. The Examiner stated that, for the reasons previously given, the priority application does not meet the requirements of 35 U.S.C. § 112, first paragraph, and therefore that the claimed invention of the present application is anticipated by Valenzuela et al.

Applicants Response

Applicants reiterate that, for the reasons discussed above, the present application meets the requirements for 35 U.S.C. § 112, first paragraph with respect to the claimed invention and that, as a continuation-in-part of application Serial No. 09/516,513 that similarly supports a specific and substantial utility and enablement for the claimed invention, the prior application likewise meets these requirements with respect to the same claimed invention. Therefore the requirements for 35 U.S.C. § 120 for claiming the benefit of the earlier filed application are met, and Valenzuela et al. therefore do not anticipate the claimed invention. Withdrawal of the rejection of claims under 35 U.S.C. § 102(b) is therefore requested

35 U.S.C. § 102(e), Rejection of Claims 1 and 3-6

The Examiner has also rejected claims 1 and 3-6 under 35 U.S.C. 102(e) as anticipated by Moore et al., U.S. Published Application 20030055236, effective filing date June 17, 1999. The Examiner stated that Moore et al. disclose a nucleic acid moecule (SEQ ID NO:22) that encodes a protein (SEQ ID NO:146) that is 100% identical to the polypeptide of SEQ ID NO:1 from amino acids 1-384 of the instant application, and therefore discloses an isolated cDNA encoding a fragment of SEQ ID NO:1 from I51-V72, G88-V109, C116-A145, I156-L175, M207-P229, or G242-T264 of SEQ ID NO:1, as recited in claim 1. Moore et al also tech vectors, host cells, and a method of making a protein, therefore anticipating claims 3-6 as well.

Applicants Response

Applicants reiterate that, for the reasons given above, the specification supports a specific and substantial utility for the claimed invention that is similarly disclosed in the priority application Serial No. 09/516,513, and providing an effective filing date for the instant application of September 17, 1998. Moore et al. therefore do not anticipate the claimed invention, at least as recited in claim 1, and withdrawal of the rejection of claims under 35 U.S.C. 102(e) is therefore requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding objections/rejections. Early notice to that effect is earnestly solicited. Applicants further submit that upon allowance of claim 1, that claims 7-12 be rejoined and examined as methods of use of the polynucleotides of claim 1 that depend from and are of the same scope, in accordance with *In re Ochiai and Brouwer* and the MPEP § 1801.04.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at the number listed below.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE CORPORATION

Date: November 5, 2003

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Attachment(s): Brenner et al. Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078
Declaration of John C. Rockett, Ph.D., under 37 CFR § 1.132, with Exhibits A-Q